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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/392,682	09/09/1999	DEITER C. GRUENERT	480.18-4	1612

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EXAMINER
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KATCHEVES, KONSTANTINA T

ART UNIT	PAPER NUMBER
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1636

DATE MAILED: 12/23/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	<b>Application No.</b> 09/392,682	<b>Applicant(s)</b> GRUENERT ET AL.	
	<b>Examiner</b> Konstantina Katcheves	<b>Art Unit</b> 1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 14 October 2005.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 17-35, 37, 38 and 40-44 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☒ Claim(s) 37 is/are allowed.
- 6) ☒ Claim(s) 17, 19-35, 38 and 40-44 is/are rejected.
- 7) ☒ Claim(s) 18 is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)  | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                                   | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)             |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____  |

### **DETAILED ACTION**

Claims 17-35, 37, 38, 40-44 are pending in the present application.

#### **I. Pending Rejections of Record**

Claims 17, 19-35, 38, 40-44 stand rejected under the enablement requirement of 35 U.S.C. 112, first paragraph for the reasons of record set forth in the Office action mailed 14 July 2005.

Claims 17, 20-26, and 28-35 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-9, 10 and 12 of U.S. Patent No. 6,010,908. This rejection is found in the Office action mailed 03 October 2001.

Any rejections not repeated herein are withdrawn.

#### **II. Response to Applicant's Arguments**

Applicants assert on page 14 of their response filed on 14 October 2005, that "much of the evidence submitted by Applicants in support of enablement was dismissed by the Examiner." Applicants previously asserted, on page 7 of Applicant's Remarks filed 26 May 2005 and in an interview with the Examiner and Primary Examiner James Ketter on 04 April 2005, that the Examiner dismissed evidence. In the prior Office action mailed 14 July 2005, as a courtesy to Applicant, the Examiner withdrew finality of the previous rejection. In an attempt to clarify the record for Applicant, the Examiner

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issued a seventeen page Office action addressing each and every piece of evidence filed by Applicant.

For Applicant's ease of consideration, the Examiner has outlined each reference and where they can be found in the table below:

Exhibit A	National Human Genome Research Institute titled "Results From First Human Gene Therapy Clinical Trial" dated 19 October 1995 (press release)	Office Action (7/14/05), Page 9 Office Action (3/26/03) Advisory Action (12/14/01)
Exhibit B	Ferber, D. Gene Therapy: Safer and Virus-Free? Science 23 November 2001 Vol. 294	Office Action (7/14/05), Page 10 Office Action (3/26/03) Advisory Action (12/14/01)
Exhibit C	Goncz et al. Expression of 38508 CFTR in normal mouse lung after site-specific modification of CFTR sequences by SFHR Gene Therapy 2001 Vol. 8 pp 951-965	Office Action (7/14/05), Page 10-11 Office Action (3/28/05) Office Action (7/13/04) Office Action (3/26/03) Advisory Action (12/14/01)
Exhibit D	Kunzelmann et al. Gene targeting of CFTR DNA in CF epithelial cells Gene Therapy 1996 pages 859-867	Office Action (7/14/05), Page 12 Office Action (3/28/05) Office Action (7/13/04)
Exhibit E	Goncz et al. Targeted replacement of normal and mutant CFTR sequences in human airway epithelial cells using DNA fragments. Human Molecular Genetics Vol. 7 no.12 1998 pages 1913-1918	Office Action (7/14/05), Page 12-13 Office Action (3/28/05) Office Action (7/13/04) Advisory Action (12/14/01)
Exhibit F	Goncz et al. Sequence specific modification of the human beta-globin gene by small fragment homologous replacement Human Gene Therapy vol. 13 2001 pp629-642	Office Action (7/14/05), Page 13 Office Action (3/28/05) Office Action (7/13/04)
Exhibit G	Goncz et al. Sequence specific modification of the human beta-globin gene by small fragment homologous replacement (SFHR), Working Group Meeting Sept. 24, 2001, abstract	Office Action (7/14/05), Page 14 Office Action (3/28/05) Office Action (7/13/04)
Declaration	Dr. Dieter C. Gruenert	Office Action (7/14/05), Page 14-15 Office Action (3/28/05) Office Action (7/13/04)

The Examiner's comments recited in each of the Office actions referred to in the table above will not be repeated herein. The Examiner will limit her response to those issues specifically raised by Applicant.

Applicant also questions the whether the Examiner's consideration the publication dates of the reference is an appropriate consideration. The Examiner is of the position that, unless the post filing date art clearly and unequivocally enable the full breadth of the invention as of the filing date sought, it is not convincing as evidence of

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enablement. Applicants should note that in spite of this position, the Examiner also addressed the substantive nature of each of the cited references in so far as they relate to the breadth of the claims.

In the present response, Applicants have failed to present any new unrebutted arguments. Applicant has organized their arguments in a claim-by-claim manner. In order to address each of Applicants' point as clearly as possible the Examiner will respond to Applicants' arguments in kind.

A. Independent claim 17.

The Examiner does not dispute that claim 17, when limited to *in vitro* methods is enabled (see claim 18). However, the breadth of claim 17 reads on *in vivo* methods and gene therapy methods for which Applicants have failed to establish enablement. Applicant argues that the record shows that "replacement of a target fragment in a cell has been demonstrated in accordance with the method of claim 17" and refers to a table of evidence which shows a list of the Exhibits and Declaration filed by Applicants. The Examiner has addressed the adequacy of each of these documents to overcome the written description requirement at length in the prior Office action. Applicants may refer to the table above to direct them to the appropriate page of the prior Office action addressing each of these references.

Applicants have failed to overcome the recognized unpredictability of the art. Methods of *in vivo* or *ex vivo* gene therapy is highly complex and unpredictable. Indeed, Applicant's own Exhibit A reinforces this position and states that "further refinement" of

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gene therapy is required and that: "as a preliminary investigation into the safety and effectiveness of gene therapy, several aspects of gene therapy remain to be perfected. One of these is more consistent methods of transporting a gene into a cell. . .". The skilled artisan at the time the present invention was made recognized the difficulty of achieving sufficient heterologous gene expression to induce any therapeutic effect.

B. Dependent Claim 18.

Dependent claim 18 is within the scope of the enable in vitro subject matter.

C. Dependent Claim 19.

With regard to claim 19, Applicant contends that Exhibit C, Exhibit F and the Declaration demonstrate successful *in vivo* fragment replacement and stable expression. Like Exhibit A cited above, Exhibit C, which is post filing date art, raises questions as to the predictability of gene therapy at the time of filing of the present application. Exhibit C discloses that those of the art are aware that *in vitro* work cannot be extrapolated to *in vivo* work: "one difficulty in going from *in vitro* to *in vivo* experiments is that the conditions relevant to transfer (the delivery vehicle, the target and the route of delivery) are different (pp.961-962 bridging paragraph)."

As previously stated by the Examiner, efficiency and sufficiency of delivery is one of the major obstacles to overcome in gene therapy; thus, the delivery vehicle used is critical. The method of Exhibit F involve the *ex vivo* modification and subsequent transplantation method of isolated cells, which fails to fully enable the claims. The *ex*

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*vivo* data fail to overcome the unpredictability of the art because they fail to show that the modification would be maintained *in vivo* because transplantation of the cells into an animal host is not shown. Additionally, the *ex vivo* data do not show that the cells would replace or out compete endogenous defective cells.

The Declaration teaches the SFHR-mediated modification of ion transport in nasal mucosa in a mouse model of cystic fibrosis. Applicant asserts that the instant declaration establishes that the present method works both *in vivo* and *ex vivo*. The declaration points to the disclosure of two exhibits in support of this position. These exhibits are discussed below. The *ex vivo* results of the Prokopishyn et al. method (Exhibit A) first fail to overcome the short coming of *in vivo* gene therapy methods. Second, regarding *ex vivo* methods, the disclosure teaches that nude mouse models were used. Another factor in the efficacy of gene therapy methods is the immune system of the host organism. Whole animals have a sophisticated immune system that must be overcome for the effective *in vivo* transfection of cells where the mouse models have compromised immune systems. The mouse models used by Prokopishyn et al. are immune compromised NOD/SCID mice wherein engraftment of transfected cells would face fewer obstacles presented by the host immune system. Even with these immuno-compromised hosts, the best data found in Prokopishyn et al. show 13 of 23 surviving mice with engrafted cell. This data, however, fails to provided direction on how to ensure that *ex vivo* modified cells method would replace, or otherwise out-compete, the endogenous defective cells and provide the desired correction.

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Goncz et al. (Exhibit B), cited in the declaration, only teach the *in vitro* microinjection of isolated human hematopoietic stem/progenitor cells and site-specific conversion of approximately 50% of these cells. The examiner does not dispute that the present method is enabled for *in vitro* practices. However, *in vitro* data does not overcome the weight of the evidence already of record that the present invention is not enabled for the full scope of the invention claimed.

D. Dependent claims 20-35 and claims 40-44

Although these claims, as stated by Applicants, recite narrower limitations of the present claims, they still fall within the broad scope of the claims and embrace *in vivo* gene delivery methods and gene therapy. As such, they remain rejected under the enablement requirement of 35 U.S.C. 112, first paragraph for the reasons already of record and those discussed above.

E. Dependent claim 37.

Given that claim 37 is drawn to an independent claim and drawn to a composition the enablement rejection as it applies to this claim is withdrawn.

F. Dependent claim 38.

Dependent claim 38 is drawn broadly to a method of gene therapy. Applicants assert that the "*in vivo* evidence of successful therapeutic application of the invention described at paragraph 6 of this Declaration [Declaration by Dr. Gruenert] has been

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overlooked (again!).” The Examiner would like to clarify, again, for the record, that the Declaration filed 28 July 2003 has been considered and discussed in the Office actions listed in the table above (Office Action mailed 7/14/05, Page 14-15; Office Action mailed 3/28/05; Office Action mailed 7/13/04).

Applicants rely on the data in paragraph 6 of the Declaration as overcoming the problem of lack of enablement for the broad scope of the invention claimed. Applicants are reminded that the scope of the claims include gene therapy and *in vivo* gene delivery methods in any animal (including human). This remains a problem in the art to this day.

The Declaration states that a 786-bp fragment of wildtype mouse CFTR is administered to the nasal mucosa of  $\Delta F508$  mice using a lipofectamine delivery vehicle. The data of the declaration is very limited and fails to enable the full scope of the invention claimed.

The data is limited to a mouse model of a specific disease, cystic fibrosis, where the genetic mutation in the gene causing the disease is known. Applicants are asking the Examiner to make several cognitive leaps with this data. The first leap would be to extrapolate the data to the therapy of any disease. The second leap would be to extrapolate the data from a mouse model for cystic fibrosis all the way to humans.

Humans are not large mice and predictions from animal models do not necessarily apply to humans. See Crystal Science Vol.270 20 October 1995 page 409, column 1. Additionally, Crystal states that not all patients in studies correcting CFTR observed correction of abnormal potential difference across the nasal epithelium. See

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page 409, col.1. The inconclusiveness in these studies shows that correction is unpredictable at best even in this narrow example of correction of abnormal potential in nasal epithelium.

Moreover, the data of the Declaration and the studies referred to by Crystal show only a correction of abnormal potential difference in nasal epithelium. For such methods to be therapeutic, as the claim of gene therapy implies requires broader application, *i.e.* more efficient gene transfer, target specificity, regulation of the target gene, sustain expression. See Crystal, page 409, column 2. These problems are also discussed in detail in the prior Office action. Applicants' data has shown some correction in the potential of cells in the nasal mucosa of  $\Delta F508$  mice that have been in direct contact with the vector, which does not overcome the problems of gene therapy discussed above and at length in the prior Office action.

For these reasons and those already of record in the prior Office action, the data of the Declaration filed 28 July 2003 and the cited Exhibits filed 03 December 2001 fail to enable the full scope of the invention claimed.

#### G. Additional Remarks.

Each of the arguments made above, although addressed individually to claims, apply to the scope of enablement rejection in general as each of the rejected claims are not enabled for their full scope.

### **III. Allowable Subject Matter**

Claim 18 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. Claim 37 is allowable.

### **IV. Conclusion**

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Konstantina Katcheves whose telephone number is (571) 272-0768. The examiner can normally be reached on Monday, Tuesday, Thursday and Friday 7:30 to 5:30.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Konstantina Katcheves  
Examiner  
Art Unit 1636



JAMES KETTER  
PRIMARY EXAMINER